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Direct and Practical Synthesis of 2-Arylbenzoxazoles Promoted by Activated Carbon

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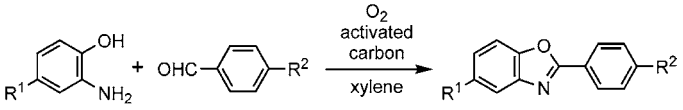
ABSTRACT



2-Arylbenzoxazoles were directly synthesized from substituted 2-aminophenols and aldehydes in the presence of activated carbon (Darco KB) in xylene under an oxygen atmosphere.

Benzoxazole ring moieties are often found in compounds that exhibit biological activities, including antitumor, antimicrobial, and antiviral properties.[1]

There are two general methods for synthesizing 2-substituted benzoxazoles. One is the coupling of 2-aminophenols with carboxylic acid derivatives, which is either catalyzed by strong acids[2] or requires microwave conditions.[3] The other is the oxidative cyclization of phenolic Schiff bases derived from the condensation of 2-aminophenols and aldehydes. In the latter reactions, various oxidants such as DDQ,[4] $Mn(OAc)_3$,[5] $PhI(OAc)_2$,[6] $Th^{+}\cdot ClO_4^{-}$,[7] $BaMnO_4$,[8] NiO_2,[9] and $Pb(OAc)_4$[10] have been used. However, all of these oxidants are required in stoichiometric or excess amounts relative to their respective substrates. Therefore, a more effective process is needed.

In this paper, we report a practical synthesis of 2-arylbenzoxazoles starting from 2-aminophenols and aldehydes under an oxygen atmosphere in the presence of activated carbon (Darco KB, Aldrich, Inc.).

We recently reported the Pd/C-catalyzed oxidative aromatization of 1,3,5-trisubstituted pyrazolines and Hantzsch 1,4-dihydropyridines, which led to the formation of pyrazoles and pyridines.[11]

In seeking to extend this system to the synthesis of 2-arylbenzoxazoles by the oxidative cyclization of phenolic Schiff bases, we first attempted to react 2-(4′-methoxybenzylideneamino)phenol (**1**) with 20 wt % of 10% Pd/C at 80 °C in acetic acid, which are suitable conditions for the reaction of pyrazolines and Hantzsch dihydropyridines. However, the desired 2-(4′-methoxyphenyl)benzoxazole (**2**) was obtained in quite low yield (9%), and the main product was a hydrolysis product of the starting Schiff base **1**.

After screening various catalysts and solvents, we found that the above oxidative cyclization proceeded even in the absence of palladium catalyst in *m*-xylene. As shown in Table

(1) (a) Deluca, M. R.; Kerwin, S. M. *Tetrahedron Lett.* **1997**, *38*, 199−202. (b) Sato, Y.; Yamada, M.; Yoshida, S.; Soneda, T.; Ishikawa, M.; Nizato, T.; Suzuki, K.; Konno, F. *J. Med. Chem.* **1998**, *41*, 3015−3021. (c) Temiz, O.; Oren, I.; Sener, E.; Yalcin, I.; Ucarturk, N. *Farmaco* **1998**, *53*, 337−341. (d) Sato, S.; Kajiura, T.; Noguchi, M.; Takehana, K.; Kobayashi, T.; Tsuji, T. *J. Antibiot.* **2001**, *54*, 102−104.

(2) Terashima, M.; Ishii, M.; Kanaoka, Y. *Synthesis* **1982**, 484−485.

(3) (a) Bourgrin, K.; Loupy, A.; Soufiaoui, M. *Tetrahedron* **1998**, *54*, 8055−8064. (b) Pottorf, R. S.; Chadha, N. K.; Katkevics, M.; Ozola, V.; Suna, E.; Ghane, H.; Regberg, T.; Player, M. R. *Tetrahedron Lett.* **2003**, *44*, 175−178.

(4) Chang, J.; Zhao, K.; Pan, S. *Tetrahedron Lett.* **2002**, *43*, 951−954.

(5) Varma, R. S.; Kumar, D. *J. Heterocycl. Chem.* **1998**, *35*, 1539− 1540.

(6) Varma, R. S.; Saini, R. K.; Prakash, O. *Tetrahedron Lett.* **1997**, *38*, 2621−2622.

(7) Park, K. H.; Jun, K.; Shin, S. R.; Oh, S. W. *Tetrahedron Lett.* **1996**, *37*, 8869−8870.

(8) Srivastava, R. G.; Venkataramani, P. S. *Synth. Commun.* **1988**, *18*, 1537−1544.

(9) Nakagawa, K.; Onoue, H.; Sugita, J. *Chem. Pharm. Bull.* **1964**, *12*, 1135−1138.

(10) Stephens, F. F.; Bower, J. D. *J. Chem. Soc.* **1949**, 2971−2972.

(11) Nakamichi, N.; Kawashita, Y.; Hayashi, M. *Org. Lett.* **2002**, *4*, 3955−3957.

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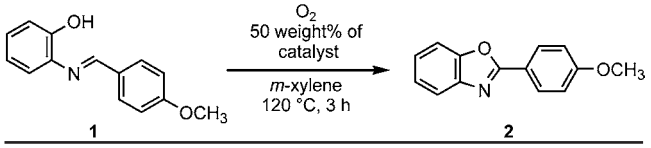
Table 1. Effect of Activated Carbon



1 2

entry	catalyst	yield/%[a]
1	activated carbon[b]	85 (0)
2	Pd/C	75 (4)
3	Pd black	27 (63)
4	none	2 (81)

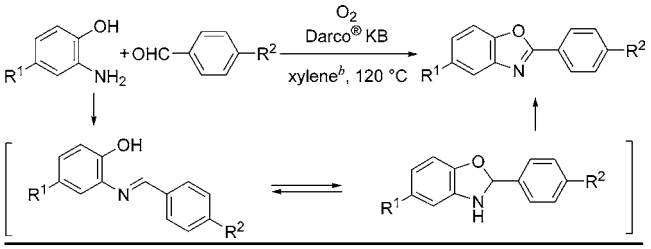
[a] ^{1}H NMR analysis. Values in parentheses indicate the yield of recovered Schiff base. [b] Darco KB (Aldrich, Inc.).

1, the reaction took place in the presence of only activated carbon (Darco KB) under an atmospheric pressure of oxygen (entry 1 in Table 1) or even under air. Thus, palladium is not necessary for this transformation, but the presence of activated carbon is crucial.

Furthermore, we found that it is not necessary to prepare Schiff bases in advance. We can use equimolar amounts of 2-aminophenols bearing substituents and aldehydes as starting materials in the presence of activated carbon (see typical procedure[12]). This direct synthesis starting from substituted 2-aminophenols and aldehydes should be synthetically useful and practical. A variety of 2-aminophenol derivatives and aldehydes can be used in this oxidative cyclization via the formation of Schiff bases, which leads to the direct synthesis of 2-arylbenzoxazoles (Table 2).

We next examined the direct synthesis of 2-phenylbenzoxazole from 2-aminophenol and benzaldehyde by using

Table 2. Direct Synthesis of Various 2-Arylbenzoxazoles[a]



entry	R^1	R^2	time/h	yield/%[c]
1	H	H	4	78[d]
2	H	CH_3	4	79[d]
3	H	OCH_3	4	76[e]
4	H	Cl	6	88[e]
5	H	CN	4	87
6	H	NO_2	4	86
7	CH_3	H	4	82[d]
8	NO_2	H	24	82
9	NO_2	OCH_3	29	67
10	NO_2	Cl	21	83

[a] Ratio of 2-aminophenols and aldehydes was 1:1; 1 g of Darco KB was used per 8 mmol (873−1233 mg) of 2-aminophenols. [b] *o*-, *m*-, *p*-xylene mixture. [c] Isolated yields by recrystallization unless otherwise noted. [d] Isolated yields by silica gel column chromatography. [e] ^{1}H NMR analysis.

three types of activated carbon with different surface areas (Darco KB, 1500 m^2/g; Darco KB-B, 1500 m^2/g; Darco G-60, 600 m^2/g) to determine whether there are any differences in reactivity. In each case, we plotted the yields of 2-phenylbenzoxazole (product), Schiff base (intermediate), and aldehyde (starting material) versus time. As shown in Figure 1, Darco KB and Darco KB-B exhibited higher

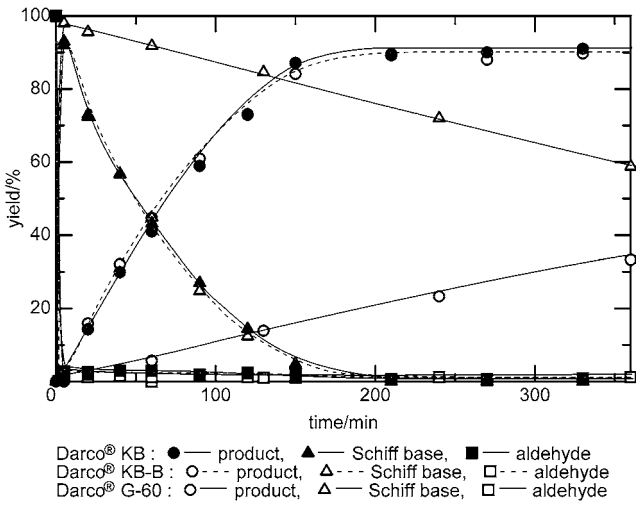


Figure 1. Time course for 2-phenylbenzoxazole, Schiff base, and aldehyde using three types of activated carbon. Reactions were performed using 2-aminophenol (0.5 mmol), benzaldehyde (0.5 mmol), and activated carbon (50 mg) in *p*-xylene-d_{10} (2 mL) at 120 °C under O_2. The yields were determined by ^{1}H NMR analysis. Anthracene (0.1 mmol) was used as an internal standard. Fe: KB (299 ppm) > G-60 (175 ppm) > KB-B (98.3 ppm). Surface area: KB (1500 m^2/g) = KB-B > G-60 (600 m^2/g) (data from Aldrich, Inc.).

activity than Darco G-60. In the reactions using Darco KB and Darco KB-B, it took about 3 h to obtain the product in 90% yield. However, the product was obtained in less than a 20% yield using Darco G-60 in the same reaction time.[13] Schiff base was formed very rapidly, and the rate-determing step was found to be oxidative cyclization.

We also measured the metal content in the above three types of activated carbon by inductively coupled plasma atomic emission spectroscopy (ICP-AES). Among the metals we examined, the content of Fe in the three types of activated carbon was Darco KB, 299 ppm; Darco KB-B, 98.3 ppm; and Darco G-60, 175 ppm. Thus, while Darco KB-B contained less Fe than Darco KB, they showed almost the

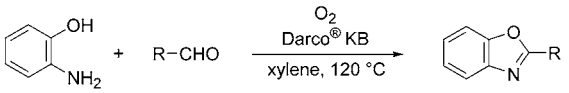
(12) **Typical Procedure** (see entry 1 in Table 2). A mixture of 2-aminophenol (873 mg, 8 mmol), benzaldehyde (849 mg, 8 mmol), and Darco KB (1 g) in xylene (15 mL) was placed in a 100 mL three-necked flask under an oxygen atmosphere and stirred at 120 °C for 4 h. The reaction mixture was then filtered using Celite. After the filtrate was concentrated, the product was isolated by silica gel column chromatography to give a pale yellow crystalline solid 1.2 g (78%). When 0.2 g of activated carbon (Darco KB) was used in the above reaction (in the same substrate scale), a longer reaction time was required (18 h, 85%).

(13) Even with Darco G-60, the product could be obtained in 96% yield with a longer reaction time (27 h).

same reactivity. Furthermore, the reactivity of Darco G-60 was quite low despite its high Fe content compared to Darco KB-B. Therefore, the surface area of the activated carbon may more strongly influence the reactivity than the amount of Fe. At present, we assume that the activated carbon effectively adsorbs oxygen to promote the reaction.

Aliphatic, as well as aromatic, aldehydes can also be used (Scheme 1). Pivalaldehyde and cyclohexanecarboxaldehyde

Scheme 1. Synthesis of 2-Alkylbenzoxazoles



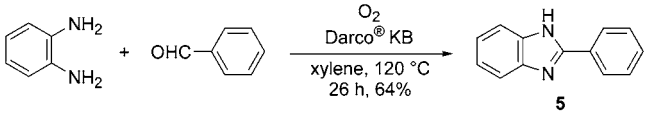
3; R = $C(CH_3)_3$, 2 h, 86%
4; R = cyclohexyl, 20 h, 33%

were reacted with 2-aminophenol to give the corresponding 2-alkylbenzoxazoles (**3**, **4**).

Furthermore, the coupling of 1,2-phenylenediamine with benzaldehyde also proceeded smoothly to give 2-phenylbenzimidazole (**5**) in 64% yield (Scheme 2).[3a,14]

In conclusion, the present method for preparing 2-arylbenzoxazoles has several advantages over conventional methods. (1) Neither metal oxides nor organic oxidizing agents are necessary. Only oxygen (or air) and inexpensive

Scheme 2. Synthesis of 2-Phenylbenzimidazole



5

and readily available activated carbon are used. (2) A direct synthesis from 2-aminophenols and aldehydes that includes the in situ preparation of Schiff bases and oxidative aromatization is achieved. It is not necessary to prepare Schiff bases in advance.[15]

Further investigations on synthetic applications and the reaction mechanism, including the role of activated carbon, are in progress.

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Supporting Information Available: Experimental procedure and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Singh, M. P.; Sasmal, S.; Lu, W.; Chatterjee, M. N. *Synthesis* **2000**, 1380−1390. (b) Beaulieu, P. L.; Haché, B.; Moos, E. *Synthesis* **2003**, 1521−1530.

(15) Present activated carbon−oxygen (or air) system was also applied to the oxidative aromatization of 1,3,5-trisubstituted pyrazolines and Hantzsch 1,4-dihydropyridines. The details will be reported soon.